UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,797	12/19/2005	Erling Sundrehagen	COCK3001-REF	4942

23364 7590 07/06/2009

BACON & THOMAS, PLLC
625 SLATERS LANE
FOURTH FLOOR
ALEXANDRIA, VA 22314-1176

EXAMINER	
FOSTER, CHRISTINE E	
ART UNIT	**PAPER NUMBER**
1641	
MAIL DATE	**DELIVERY MODE**
07/06/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,797	SUNDREHAGEN, ERLING	
	Examiner	Art Unit	
	CHRISTINE FOSTER	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-24,26 and 28* is/are pending in the application.

4a) Of the above claim(s) *20-24 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-19 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment, filed 4/29/2009, is acknowledged and has been entered. Claims 14-24 and 26 were amended. New claim 28 has been added.

Election/Restrictions

2. Claim 26, as amended in the instant Reply, is now directed to an invention that lacks unity with the invention originally claimed for the following reasons:

As originally filed, claim 26 recited a method for "diagnosis of a disease". As amended in the instant Reply, claim 26 now recites a method "for assessing the potential for or propensity to cardiovascular disease". The currently presented claim therefore relates to the prediction of future cardiovascular disease, while the originally presented claim related to diagnosis of existing disease (see also Applicant's remarks in the instant Reply, pages 8-9). In addition, the claim now recites an additional step in which calprotectin levels above a threshold value are correlated with an indication of potential for or propensity to cardiovascular disease.

In the requirement for restriction mailed 3/14/2008, Applicant was given the opportunity to elect methods for the detection of potential or propensity for CVD (see Group I, page 2 of the restriction requirement). However, methods for diagnosis of disease (Group III) were instead elected for consideration. The instant amendments to claim 26 mean that the claim now reads on non-elected Group I rather than on elected Group III.

Unity of invention is reassessed at each stage of prosecution. The currently presented claim 26, directed to assessing the potential for or propensity to cardiovascular disease, shares in

common with the originally elected Group III the technical feature of an assay method for the determination of calprotectin as claimed in claim 14.

According to PCT Rule 13.2, unity of invention exists only when the shared same or corresponding technical feature is a contribution over the prior art. For reasons set forth in detail under § 103 below, the assay method of claim 14 is not found to represent a contribution over the prior art. Consequently, claim 26 as instantly amended lacks unity with the invention originally claimed.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 26 is withdrawn from consideration as being directed to a nonelected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Unity of invention will be reassessed at each stage of prosecution hereafter.

Manner of Making Amendments under 37 CFR 1.121

3. In the interest of expediting prosecution, Applicant's submission has been accepted. However, Applicant is reminded of the proper format for amendments to the claims. Specifically, claim 27 has been presented with the status identifier "Cancelled", yet the text of the claim is also presented. No claim text shall be presented for any claim in the claim listing with the status of "canceled". See MPEP 714.

Status of the Claims

4. Claims 14-24, 26, and 28 are pending in the application, with claims 20-24 and 26 currently withdrawn. Claims 14-19 and 28 are subject to examination below.

Priority

5. The present application was filed on 12/19/2005 as a proper National Stage (371) entry of PCT Application No. PCT/GB03/05607, filed on 12/23/2003. Acknowledgment is also made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to Application No. 0229747.1, filed on 12/20/2002 in the United Kingdom.

Objections/ Rejections Withdrawn

6. The objections to the specification have been withdrawn in response to Applicant's amendments thereto.

7. The objections to and rejections of claim 26 are moot in light of the withdrawal of this claim from examination (see above).

8. The objections to claims 14-19 and 25 as set forth in the previous Office action have been withdrawn in response to Applicant's amendments.

9. The rejection of claim 27 is moot in light of Applicant's cancellation of the claim.

10. The rejections under § 112, 2nd paragraph not reiterated below have been withdrawn.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 14-19, 26, and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. Claim 14 recites that the diameter of the antibody or antibody fragment-coated nanoparticles is "**in the range 65-140 nm**". The use of the terminology "in the range" renders the indefinite because it is unclear whether Applicant intends "in the range" to refer to the specific range of 65-140 nm, or alternatively whether the words "in the range" are meant as a qualifying statement indicating that the recited range is to be taken as approximate. In particular, the metes and bounds of the claims are unclear because it is not apparent whether only particles of diameter 65-140 nm would be included or also those having a diameter that approximates or is "in the range" of this range.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 14-19 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arvesen et al. ("Calprotectin: A Novel Plasma Marker of Granulocyte Activation in Acute Coronary Syndrome"; Circulation 1996; Vol 94(8), page 3015) in view of Craig et al. (US 4,480,042), or, in the alternative, as being unpatentable over Craig et al. in view of Arvesen et al.

Arvesen et al. teach that calprotectin is a marker of granulocyte activation in the context of acute coronary syndrome (title). Arvesen et al. studied patients with acute coronary syndrome (including unstable angina and non-Q myocardial infarction) and found that the patients had elevated levels of calprotectin in plasma as compared to healthy controls (see entire selection).

Arvesen et al. do not provide details regarding the assay method used to measure calprotectin, and therefore fail to specifically teach turbidimetric assessment using a nanoparticle of diameter 65-140 nm that is bound to a calprotectin antibody.

Craig et al. teach particle-based immunoassay methods, in which changes in turbidity caused by agglutination of particles can be used to measure unknown concentrations of compounds of biological interest (the abstract). The particles of Craig et al. have approximate diameter range of 0.03-0.1 μm (30-100 nm, i.e., "nanoparticles") and may have an antibody to the compound of interest covalently attached thereto (column 2, line 45 to column 5, line 32). For example, antibody particle reagents can be used in a direct particle enhanced turbidimetric immunoprecipitation assay, which provides increased detectability over conventional immunoprecipitation techniques, corresponding savings in reagent costs, and also allows for the use of smaller patient sample volumes (column 9, lines 23-33). Craig et al. also teach that turbidity measurements of immunological reactions using their particles are advantageous in that no special equipment is required other than a spectrophotometer (column 4, lines 59-63).

Therefore, it would have been obvious to one of ordinary skill in the art to determine the calprotectin in plasma as taught by Arvesen et al. using the particle-based turbidimetric immunoassay methods of Craig et al. In particular, it would have been obvious to coat the particles of Craig et al. with an antibody specific for calprotectin and to determine the

calprotectin content in the plasma samples by measuring changes in turbidity. The selection of a known method for its known purpose (detection of an unknown concentration of a substance of interest in a biological fluid sample) would have been obvious. In addition, one would have been motivated to employ the assay methods of Craig et al. because Craig et al. taught that such methods do not require special equipment, provide increased detectability over conventional immunoprecipitation techniques, savings in reagent costs, and also allow for the use of smaller patient sample volumes, which would be particularly pertinent to the methods of Arvesen et al. in which calprotectin was measured in patient samples.

Regarding the limitation that the diameter of the antibody or antibody fragment-coated nanoparticles is in the range 65-140 nm, Craig et al. exemplifies particles having a diameter of 69 nm (Example 1, see especially at column 10, lines 57-58). However, Craig et al. do not indicate what size their particles would have after being coated with antibody.

However, the instant specification discusses on page 19 how the diameter of the particles may be measured either before or after the antibodies are bound to their surface: particle size ranges of 55-140, 65-110, and 70-90 nm are disclosed for "nude" particles, and size ranges of 65-140, 75-120, and 80-110 nm are disclosed for antibody-coated particles. Such teachings indicate that coating of an antibody would result in an approximate 10-nm increase in particle size diameter; i.e., from 69 to 79 nm in the case of the Craig et al. particles.

For these reasons, there is a strong scientific basis to believe that the particles of Craig et al., when coated with antibody, would have a diameter falling within the claimed ranges of 65-140 nm and 75-120 nm as recited in instant claims 14-15. Because the claimed and prior art

products appear to be identical or substantially identical, Applicant has the burden of advancing evidence to show that they are not. See MPEP 2112.

Notwithstanding the above, the Examiner also notes that Craig et al. teach that it is important to select the particle size with care in order to optimize the turbidity change which occurs during agglutination (column 5, lines 1-2). Given this recognition of particle size as a result-effective variable, it would also have been obvious to arrive at the claimed size ranges out of the course of routine optimization, given the normal desire of artisans to improve upon what is already known. See MPEP 2144.05.

One would have a reasonable expectation of success because Craig et al. taught that their particle-based immunoassay methods can be used for detecting a wide variety of substances in biological fluids (including plasma). See column 9, lines 8-22.

It is also possible to analyze the teachings of Craig et al. in view of those of Arvesen et al. Craig et al. teach an assay method for the determination of compounds of interest in biological samples, comprising the steps of obtaining a biological fluid sample, contacting the sample with a nanoparticle-bound antibody specific for the compound of interest; and assessing the concentration of the compound of interest by turbidimetry. See passages noted above and claim 1 in particular.

The Craig et al. reference differs from the claimed invention, however, in that the reference fails to teach determination of the analyte calprotectin.

However, in light of the teachings of Arvesen et al. that calprotectin is a marker of granulocyte activation in acute coronary syndrome, it would have been obvious to one of ordinary skill in the art to employ the assay method of Craig et al. to determine calprotectin as an

analyte of clinical interest. In particular, it would have been obvious to coat the particles of Craig et al. with an anti-calprotectin antibody and to determine the calprotectin concentration in plasma samples.

With respect to claims 16 and 28, Craig et al. teach that the final particle size is controllable and is substantially uniform, i.e. monodisperse (column 5, lines 20-25).

With respect to claim 17, Craig et al. teach that the agglutination reaction can be accelerated by the presence of an agglutinating enhancer (i.e., an opacity enhancer) such as polyetheylene glycol or sodium dodecyl sulfate (column 10, lines 16-22 and claims 2-3). Although Craig et al. do not specifically teach when the enhancer is added, the selection of any order of mixing ingredients would have been prima facie obvious. See MPEP 2144.04(C).

With respect to claim 19, Craig et al. exemplify use of a clinical analyzer instrument in performing their assay methods (Example 5, see especially column 12, lines 39-56). It would have been further obvious when performing the particle-based turbidimetry immunoassay for calprotectin of Craig et al. and Arvesen et al. to similarly employ a clinical analyzer, which would be considered to be an "automated" assay absent a specific or limiting definition in the instant specification.

In addition, the courts have ruled that broadly providing an automatic or mechanical means to replace a manual activity which accomplishes the same result is not sufficient to distinguish over the prior art. See MPEP 2144.04(III). Therefore, when taken together with the general knowledge in the art, it would also have been obvious to automate the assay method of Craig et al. and Arvesen et al.

Response to Arguments

16. Applicant's arguments filed 4/29/2009 have been fully considered.

17. With respect to the rejection of claim 14 under § 112, 2nd paragraph for reciting that the diameter of the antibody or antibody fragment-coated nanoparticles is "**in the range 65-140 nm**", Applicant argues that this term has been deleted from claim 14 (Reply, page 7). However, no corresponding amendments could be found as part of the currently presented claim set. Accordingly, the rejection is maintained for reasons of record.

18. With respect to the rejections under § 103 as being unpatentable over Arvesen et al. in view of Craig et al. (or alternatively over Craig et al. in view of Arvesen et al.), Applicant's arguments (Reply, pages 7-10) have been fully considered but are not persuasive.

Applicant acknowledges that it was known at the time of the invention that calprotectin was elevated in patients who had suffered a serious cardiovascular event. However, Applicant argues that Arvesen relates to patients with pre-existing conditions but does not disclose calprotectin as a marker for the potential or propensity for cardiovascular disease or as a predictor of cardiovascular disease status (Reply, paragraph bridging pages 8-9).

The Examiner notes that such remarks appear to be directed only to the invention of claim 26, as claims 14-19, and 28 do not refer to cardiovascular disease at all.

Consequently, Applicant's arguments are acknowledged but are moot as claim 26 is currently withdrawn from examination.

Applicant further argues that the method of Craig is a competitive method that is not highly suitable for calprotectin, while the instant invention is not a competitive assay method and does not employ a calprotectin analog (Reply, pages 9-10). This is not found persuasive because

the claims employ open transitional language ("An assay method…comprising") that permit additional unrecited steps or elements (such as the use of a calprotectin analog). There is nothing in the claims that would exclude or distinguish over competitive assay methods such as those of Craig et al.

Applicant further argues that the method of Craig et al. is not suitable for assaying calprotectin at relevant concentrations and would not provide useful clinical information (Reply, pages 9-10).

This is not found persuasive because to be of probative value, any objective evidence should be supported by actual proof. Objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence inoperability of the prior art. See MPEP 716.01(c). Arguments of counsel cannot take the place of factually supported objective evidence. See, e.g., In re Huang, 100 F.3d 135, 139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); In re De Blauwe, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984).

In the instant case, Craig et al. taught that their particle-based immunoassay methods can be used for detecting a wide variety of substances in biological fluids, including plasma. See column 9, lines 8-22. Therefore, while the arguments of counsel have been considered, they do not constitute sufficient evidence that the method of Craig et al. is not suitable for assay of calprotectin.

In addition, the instant claims are not limited to measurement of any particular concentration range of calprotectin. Consequently, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon

which applicant relies (i.e., assay of calprotectin at "relevant concentrations") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Conclusion

19. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/
Examiner, Art Unit 1641

/Christopher L. Chin/
Primary Examiner, Art Unit 1641